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Mechanism of Developing Hypertension with Longevity via Renal Sodium Transporters.

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Summary

Introduction: Hypertension is a common disease with more than 20 million patients throughout Japan. The number of hypertensive patients increases with age, and salt sensitivity. Furthermore, salt sensitivity and aging are expected to exacerbate hypertension mutually. We focused on the renal tubular sodium (Na) transporter NBCe1 and demonstrated the magnitude of sodium handling with mutations in NBCe1 using functional analysis techniques. We also focused on the regulatory mechanisms of hypertension via mineralocorticoid receptor (MR), located in the distal tubular and collecting duct. The purpose of this study is to elucidate the integrated regulatory mechanism of the Na transport system in the kidney tubule and its relationship between hypertension and aging.

Methods: 1) Novel identified novel single nucleotide variant (SNV) of NBCe1: We surveyed the transmembrane domain of Na transporter NBCe1, using the Polyphen-2 prediction tool. 2) Identified SNVs on MR: We hypothesized that the Ligand Binding Domain (LBD) at the C-terminus of MR is an important site for binding Aldo. We searched SNVs in MR that induce potent sodium reabsorption. 3) Generation of ULK1 knockout (KO) mice: ULK1-KO mice are considered an autophagy-impaired model, leading to accelerated hypertension and aging.

Results: 1) We newly identified a novel loss-of-function SNV, R881S, located in transmembrane 12. R881S SNV was distributed only in the cytosol and lacked a dominant negative effect. Functional analysis using the two-electrode voltage clamp method showed that R881S transport activity was completely abolished. 2) We identified approximately 50 SNVs in the LBD area, potentially regulating the blood pressure system. 3) The amount of ULK1 protein decreased with aging in ULK1-KO mice, suggesting that ULK1 is an important factor in the regulation of aging.

Discussion: These findings support that the Na transport system contributes to hypertension. We need to investigate the relationship between SNVs and hypertension accelerated by aging.